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EXAMINER

ROYDS, LESLIE A

ART UNIT

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1614

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 09/659,643	Applicant(s) GIBBONS JR. ET AL.	
	Examiner Leslie A. Royds	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 January 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 15 and 18 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 15 and 18 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Claims 15 and 18 are presented for examination.

Applicant's Amendment filed January 22, 2008 has been received and entered into the present application.

Claims 15 and 18 remain pending, amended and under examination. Claims 16-17 are cancelled.

Applicant's arguments, filed January 22, 2008, have been fully considered. Rejections and objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description Requirement

(New Grounds of Rejection)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15 and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Present claim 15 is newly amended to read on an improved method of treating a non-small cell lung tumor in a mammal which comprises administering to said mammal an effective amount of a combination comprising a cytokine inducer and a chemotherapeutic agent, wherein the cytokine inducer is [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]L-lysyl]-alanine or a pharmaceutically acceptable salt thereof, wherein the chemotherapeutic agent is

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selected from the group consisting of paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, doxorubicin, cisplatin, carboplatin, mitomycin C, bleomycin and a combination thereof, and wherein said combination of the cytokine inducer and the chemotherapeutic agent or chemotherapeutic agents has a greater tumor suppressing effect than that of the chemotherapeutic agent or chemotherapeutic agents alone. Present claim 18 is directed to the use of paclitaxel or carboplatin or a combination thereof as the chemotherapeutic agent(s).

In particular, the specification and claims as originally filed fail to provide adequate written description for the limitation directed to “wherein said combination of the cytokine inducer and the chemotherapeutic agent or chemotherapeutic agents has a greater tumor suppressing effect than that of the chemotherapeutic agent or chemotherapeutic agents alone” (claim 15), or further wherein such an effect is achieved using carboplatin alone (claim 18).

MPEP §2163 states, “The courts have described the essential question to be addressed in a description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement is, “does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed.” *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test of sufficiency of support in a parent application is whether the disclosure of the application relied upon “reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter.” *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983))...Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys

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with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)."

Applicant discloses at p.2, 1.12-20 of the instant specification that, "This invention provides a method of treating solid tumors which comprises administering an effective amount of a combination of (1) a bioresponse modifier and (2) a chemotherapeutic agent. This invention also provides a method of potentiating the effects of a chemotherapeutic regimen in a mammal in need of treatment with such regimen which comprises administering a bioresponse modifier in addition to a chemotherapeutic regimen. As used in this invention, the term a bioresponse modifier and a chemotherapeutic agent includes the administration of one or more agents of each category; thus, for example, the term a chemotherapeutic agent can include the administration of two chemotherapeutic agents."

Still further, the specification further discloses an example at p.5-6, wherein the combination of paclitaxel and [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]L-lysyl]-alanine was administered to mice with non-small cell lung cancer xenografts (p.5). Results reported from the example showed enhanced tumor suppression when [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]L-lysyl]-alanine was administered one day following paclitaxel administration as compared to the untreated control group or the paclitaxel only group. Similar tumor mass reducing effects were seen using carboplatin and paclitaxel in combination with [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]L-lysyl]-alanine versus untreated control or paclitaxel and carboplatin alone (see, e.g., p.7 of the instant specification).

However, such disclosure of the potentiating effect of bioresponse modifiers on chemotherapeutic agents or the particular disclosure of an enhanced tumor suppressing effect when using the cytokine inducer compound [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-

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ethoxy]carbonyl]L-lysyl]-alanine with either paclitaxel or paclitaxel with carboplatin fails to provide adequate written support to now narrow the claims to (1) a greater tumor suppressing effect using the cytokine inducer [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]L-lysyl]-alanine in combination with any chemotherapeutic agent over that seen using the chemotherapeutic agent alone (claim 15) or (2) a greater tumor suppressing effect using the cytokine inducer [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]L-lysyl] alanine in combination with carboplatin alone. This is a clear narrowing of the subject matter both claimed and disclosed in the specification and claims as originally filed that is not adequately supported, either explicitly or implicitly, by the original disclosure because (1) the disclosure of “potentiating the effects of a chemotherapeutic agent” fail to identify the specific “effect” of the chemotherapeutic agent that is, in fact, potentiated and (2) the disclosure of an enhanced tumor suppressing effect seen with paclitaxel or paclitaxel and carboplatin in combination with the claimed cytokine inducer fails to provide written support for the same effect using any chemotherapeutic agent. It is clear, therefore, that Applicant was not in possession of the concept of eliciting a greater tumor suppressing effect using the claimed cytokine inducer with *any* chemotherapeutic agent, but rather was solely in possession of the concepts of (1) potentiating the effect of chemotherapeutic agents using a combination of bioresponse modifier compound with a chemotherapeutic agent or (2) a greater tumor suppressing effect using the claimed cytokine inducer compound [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]L-lysyl]-alanine with either paclitaxel or paclitaxel with carboplatin as the chemotherapeutic agent.

As stated in MPEP §2163, “The subject matter of the claim need not be described literally (i.e., using the same terms of *in haec verba*) in order for the disclosure to satisfy the description requirement.” However, considering the teachings provided in the specification as originally filed, Applicant has failed to provide the necessary teachings, by describing the claimed invention, in such a way as to reasonably

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convey to one skilled in the relevant art that Applicant had possession of the limitation directed to “wherein said combination of the cytokine inducer and the chemotherapeutic agent or chemotherapeutic agents has a greater tumor suppressing effect than that of the chemotherapeutic agent or chemotherapeutic agents alone” (claim 15) or further wherein such an effect is achieved using carboplatin alone (claim 18).

Accordingly, the claims are considered to lack sufficient written description and are properly rejected under 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 112, Second Paragraph (New Grounds of Rejection)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claim 15 is directed to an improved method of treating a non-small cell lung tumor in a mammal, comprising administering to said mammal an effective amount of a combination comprising a cytokine inducer and a chemotherapeutic agent, wherein the cytokine inducer is [R-(R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]L-lysyl]-alanine or a pharmaceutically acceptable salt thereof, wherein the chemotherapeutic agent is selected from the group consisting of, *inter alia*, paclitaxel, etc. and wherein said combination of the cytokine inducer and the chemotherapeutic agent or chemotherapeutic agents has a greater tumor suppressing effect than that of the chemotherapeutic agent or chemotherapeutic agents alone.

In particular, the term “improved” in the phrase “improved method” in claim 15 is a relative term which renders the claim indefinite. The term “improved” is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would

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not be reasonably apprised of the scope of the invention because it is unclear from the claimed context what type and degree of improvement is intended and how it would be determined. In addition, though the claim states that the combination of the cytokine inducer and the chemotherapeutic agent provides a greater tumor suppressing effect than that of the chemotherapeutic agent alone, the claim fails to clearly, precisely or deliberately set forth whether this, in fact, is what is intended to be the improvement of the claimed method or, for example, the "improvement" is simply the use of the claimed cytokine inducer with a chemotherapeutic agent. As a result, the claims fail to clearly, precisely or deliberately set forth the parameter that is intended to be indicative of improvement, how it is to be measured and what standard would be used to make such a comparison to determine whether the improvement has been achieved. Absent this information, the claims clearly fail to set forth the metes and bounds of the subject matter for which Applicant is presently seeking protection.

Furthermore, there is insufficient antecedent basis for the limitation "the...chemotherapeutic agents" (note that the word "the" in line 9 of the claim is understood to modify both "chemotherapeutic agent" and "chemotherapeutic agents") in line 9 of claim 15, since the preceding text of the claim fails to set forth any reference to "chemotherapeutic *agents*" *per se*.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

Claim Rejections - 35 USC § 103 (New Grounds of Rejection)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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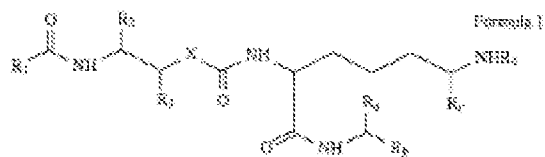
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 15 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Francis et al. ("Paclitaxel (Taxol) and Docetaxel (Taxotere): Active Chemotherapeutic Agents in Lung Cancer", *Lung Cancer*, 1995, 12 Suppl.1:S163-S172) in view of Aryal-Kaloustian et al. (U.S. Patent No. 5,545,662; 1996).

Francis et al. teaches that docetaxel is among the most active chemotherapeutic agents for non-small cell lung cancer patients (abstract). Francis et al. teaches that the dose-limiting toxicity for docetaxel in Phase I studies in lung cancer patients was neutropenia (Sect. 3, p.S166) and further teaches that neutropenia was also the most common toxicity observed in Phase II clinical trials of docetaxel in advanced non-small cell lung cancer patients (Sect. 4, p.S166-167).

Francis et al. fails to teach the concomitant use of the claimed cytokine inducer compound, [R-R*,R*)]-N-[(R)-6-carboxy-N²-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy]carbonyl]-L-lysyl]-D-alanine, with the docetaxel therapy for treating non-small cell lung cancer to result in a greater tumor suppressing effect than the docetaxel alone (claim 15).

Aryal-Kaloustian et al. teaches urea and urethane compounds of the formula



or pharmaceutically acceptable salts thereof (col.2, 1.41-

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42), of which the specific compound [R-(R*,R*)]-N-[(R)-6-carboxy-N2-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy]carbonyl]-L-lysyl]-D-alanine is exemplified (Ex.28, col.31, l.1-20), for use in restoring neutrophils after cancer chemotherapy by inducing endogenous production of IL-6 and GCSF growth factors, each of which are known to regulate neutrophil production in the bone marrow (col.19, l.18-31; see also Tables 1-3 at cols.19-20). In fact, Aryal-Kaloustian et al. expressly teaches a study of the compound of Example 28 (identical to Applicant's claimed cytokine inducer; see col.31, l.1-20), which demonstrated synergistic activity *in vitro* with c-kit ligand in enhancing the growth of bone marrow progenitor cells, which was understood to support the claim that this compound acted to enhance the growth of neutrophil progenitor cells in the bone marrow (col.19, l.5-15).

In view of such teachings, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to combine the cytokine inducer compound of Aryal-Kaloustian et al., [R-(R*,R*)]-N-[(R)-6-carboxy-N2-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy]carbonyl]-L-lysyl]-D-alanine, with the docetaxel therapy of Francis et al., to ameliorate the dose-limiting neutropenic toxicity that frequently occurs in non-small cell lung cancer patients receiving treatment with docetaxel by providing neutrophil rescue and enhanced neutrophil production in the bone marrow via production of IL-6 and GCSF, each of which stimulates neutrophil generation. Further, the use of a multivalent therapy comprising an effective chemotherapeutic agent (i.e., docetaxel) in combination with an effective neutropenia-ameliorating agent would have been *prima facie* obvious to one of ordinary skill in the art treating patients suffering from non-small cell lung cancer. Such a person would have been motivated to do so not only to provide the cancer patient with an effective chemotherapeutic agent (i.e., docetaxel), but also to provide this particular subpopulation of patients concomitantly suffering from neutropenia as a result of their chemotherapy an effective pharmacologic means of treating the neutropenia by using a known cytokine inducer compound, such as the compound of Aryal-Kaloustian et al. This is because it is generally *prima facie* obvious to use, in combination, two or more agents to treat multiple symptoms

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resulting from the same condition in order to provide a means of ameliorating the medical condition that triggered such symptoms, and further thereby improving the patient's overall health.

Though it is noted that such a reason to combine the docetaxel therapy of Francis et al. for treating a non-small cell lung cancer tumor in a mammal with the cytokine inducer compound of Aryal-Kaloustian et al. (i.e., [R-(R*,R*)]-N-[(R)-6-carboxy-N2-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy]carbonyl]-L-lysyl]-D-alanine) does not explicitly teach that the tumor suppressing effect of the combination (i.e., the cytokine inducer plus the chemotherapeutic agent) is greater than that achieved using the chemotherapeutic agent alone as now instantly claimed, Francis et al. provides a clear teaching that the instantly claimed chemotherapeutic agent(s) (i.e., docetaxel) is, in fact, effective for treating all patients exhibiting a non-small cell lung tumor, without exclusion. Of this entire non-small cell lung cancer (herein after "NSCLC") population, Francis et al. further provides a clear teaching that a subpopulation of NSCLC patients also suffer concomitantly from neutropenic toxicity as a result of such chemotherapy. Accordingly, one of ordinary skill in the art at the time of the invention would have been clearly motivated to employ a neutropenic rescue agent, i.e., the cytokine inducer of Aryal-Kaloustian et al. ((i.e., [R-(R*,R*)]-N-[(R)-6-carboxy-N2-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy]carbonyl]-L-lysyl]-D-alanine) to treat this subpopulation of NSCLC patients with dose-limiting neutropenic toxicity to enhance neutrophil production and restore normal neutrophil function. In other words, the art cited *supra* clearly provides a motivation to use both the claimed cytokine inducer and the claimed chemotherapeutic agent (i.e., docetaxel) together to treat an NSCLC patient, absent factual evidence to the contrary. Since products of identical composition (i.e., in this case, the combination of the claimed cytokine inducer with the claimed chemotherapeutic agent) cannot have mutually exclusive properties when administered under identical conditions, or, as in the present case, the same NSCLC host, whatever functional effect(s) the instantly claimed combination has in enhancing tumor suppressing effect must reasonably be expected to occur in the method suggested by the cited

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references to Francis et al. in view of Aryal-Kaloustian et al., absent factual evidence to the contrary. Please see MPEP §2112.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the Applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the newly cited function at the time of invention, so long as the subject matter stated to be present in the normal and usual course of execution of the disclosed method is, indeed, reasonably expected to be present. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention"). Note that, even though *Toro* was decided in the context of inherent anticipation, considerations of inherent teachings arise both in the context of anticipation and obviousness (see, e.g., *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995) or *In re Grasselli*, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983) and MPEP §2112).

Response to Applicant's Arguments

Applicant states that the compound of formula I (understood to be the cytokine inducer taught by Aryal-Kaloustian et al.) lacks efficacy in treating cancer, anti-tumor activity is not an inherent property and, thus, one of skill in the art would have no motivation to combine the urea compound (i.e., the compound disclosed by Aryal-Kaloustian et al.) with a chemotherapeutic agent for treating an NSCL

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tumor. Applicant further urges the surprising potency of the cytokine inducer and the chemotherapeutic agent in reducing tumor mass size as shown in Table 1 (p.6 of the instant specification), as well as the tumor mass reduction seen using the combined therapy of paclitaxel, carboplatin and the cytokine inducer.

Applicant's remarks have been fully and carefully considered, but fail to be persuasive.

Firstly, with regard to Applicant's argument that there is a lack of motivation to combine the urea compound disclosed by Aryal-Kaloustian et al. (i.e., synonymous with the instantly claimed cytokine inducer) with a chemotherapeutic agent for treating an NSCL tumor, Applicant's attention is directed *supra* to the specific statements of motivation and rationale as to why one of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to combine the instantly claimed cytokine inducer with a chemotherapeutic agent, such as, e.g., docetaxel as disclosed by Francis et al. Such reasons will not be repeated herein for the sake of brevity. Furthermore, though it may very well be true that the cytokine inducer lacks efficacy in treating cancer *per se*, the motivation as provided *supra* regarding the obviousness of making such a combination does not, in fact, rely upon the cytokine inducer to provide anti-cancer efficacy, but rather to provide neutropenic rescue as a result of docetaxel therapy (which, as evidenced by Francis et al., results in neutropenia). In other words, although the cytokine inducer may be devoid of anti-cancer efficacy *per se*, such is immaterial to the fact that one of skill in the art at the time of the invention would have been clearly motivated to combine the two compounds to treat the neutropenia that occurs as a result of docetaxel administration and, thus, would have been reasonably expected to exhibit the same (or at least substantially similar) enhanced tumor suppressing effect over the chemotherapeutic agent alone when administered to the same NSCLC patient, absent factual evidence to the contrary.

Secondly, Applicant's Examples presented in summary Tables 1 and 2 (see p.5-8 of the instant specification) have been fully and carefully considered, but fail to support the allegation of unexpected

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results *commensurate in scope* with the presently claimed subject matter. It is not disputed that, according to the results of tumor mass size for each of the exemplified combinations (i.e., paclitaxel with cytokine inducer or paclitaxel, carboplatin and cytokine inducer), a synergistic effect was demonstrated for each of these two specific embodiments in non-small cell lung mouse xenografts. However, both the instant specification and Applicant's remarks presented in the amendment of January 22, 2008 each conspicuously fail to present any discussion of how these two discrete examples reasonably correlate to the full scope of chemotherapeutic agent and cytokine inducer combinations presently claimed such that the skilled artisan would have been imbued with at least a reasonable expectation of success in achieving this same allegedly unexpected effect over the entire scope of the presently claimed subject matter.

The omission of such a discussion of how these two embodiments are suggestive of any results beyond the scope of what has been exemplified fails to provide any basis for interpreting the specific agents used in the proffered Examples to be suggestive of at least a reasonable expectation of achieving the same, or substantially similar, synergistic effect over the full scope of agents instantly claimed. In the absence of such discussion, evidence, and/or scientific reasoning to this effect, Applicant's allegations of synergism and non-obviousness of the claimed subject matter fail to be probative of non-obviousness of the full scope of the claimed subject matter and, therefore, do not, in fact, outweigh the evidence of obviousness because Applicant has failed to identify how the evidence presented in the specific examples of the specification may be reasonably extrapolated to the full scope of subject matter (i.e., in particular, the full scope of chemotherapeutic agents to be used in combination with the claimed cytokine inducer) presently claimed as being suggestive of similarly unexpected synergistic activity.

Though Applicant urges that these unexpected results be given their due weight, Applicant is first reminded that (1) the instant claims are not limited solely to the specific conditions of the embodiments for which Applicant demonstrated the synergistic effect (i.e., by limiting to the specific combinations exemplified, such as paclitaxel and cytokine inducer or paclitaxel, carboplatin and cytokine inducer) and

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(2) Applicant has provided no discussion, evidence or scientific reasoning as to why such embodiments for which Applicant has demonstrated synergistic reduction in tumor mass are probative of the same (or at least substantially similar) synergistic effect over the full scope of conditions presently claimed. Given these facts, it is clear that Applicant has failed to demonstrate synergy commensurate with the breadth of the instant claims. As a result, the claims as presently written clearly encompass embodiments wherein an unexpectedly synergistic effect has not been demonstrated and, therefore, do not distinguish over the effect that would have been already *expected* from the prior art as evidenced by the reasoning provided in the grounds of the instant rejection set forth *supra*.

Accordingly, it remains that the instant claims still encompass embodiments for which synergy and/or unexpected activity has not been demonstrated (i.e., the combination of docetaxel with the claimed cytokine inducer) and, therefore, remain obvious in view of the cited prior art, which provides *at least a reasonable expectation* of achieving the claimed enhanced tumor suppressing activity when the claimed cytokine inducer is used in combination with docetaxel for treating NSCLC patients with neutropenia as a result of docetaxel therapy. Though Applicant relies upon the results of the instant examples to demonstrate that synergism would be expected over the full scope of combinations of chemotherapeutic agents as claimed with the claimed cytokine inducer, it is again noted that Applicant's synergistic result of Tables 1 and 2 is not disputed by the Examiner. However, as discussed *supra*, this evidence of synergism was demonstrated using two discrete combinations of cytokine inducer and chemotherapeutic agent (i.e., paclitaxel and cytokine inducer or paclitaxel, carboplatin and cytokine inducer) and, absent any reasons or evidence to support the extrapolation beyond these limited combination(s), fails to provide evidence of synergism commensurate in scope with the breadth of the claims. In view of this fact, it is maintained that Applicant has not demonstrated synergism over the full scope of the claims and is, therefore, attempting to predict synergism beyond what was demonstrated in the absence of supporting data, evidence or rationale to support the same.

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Furthermore, Applicant is reminded that she bears the burden of explaining the proffered data as being evidence of non-obviousness over the full scope of the claimed subject matter and why the evidence provided to support secondary considerations is probative of non-obviousness beyond what data is explicitly provided as unexpected (i.e., over the full scope of the claims). In other words, Applicant bears the responsibility of explaining why the unexpected activity demonstrated with the specific combinations of agents (i.e., paclitaxel and cytokine inducer or paclitaxel, carboplatin and cytokine inducer) used in the Examples at pages 5-8 of the specification is probative of the same, or at least substantially similar, unexpected activity when the combination is administered according to the claims as presently written, which encompass numerous combinations of the claimed cytokine inducer with any one or more of the chemotherapeutic agent(s) instantly claimed. Please see MPEP §716.02(b)[R-2], particularly Section (II), which states, “[A]ppellants have the burden of explaining the data in any declaration they proffer as evidence of non-obviousness.” *Ex parte Ishizaka*, 24 USPQ2d 1621, 1624 (Bd. Pat. App. & Inter. 1992). This required explanation, however, is not satisfied merely by Counsel's assertions that the same activity would be expected beyond the data that is provided as evidence of unexpected activity.

The issue at hand is not that Applicant has failed to demonstrate a synergistic effect as evidenced in Tables 1-2 of Applicant's specification, but rather that this same synergistic effect was elicited using two specific combinations of agents and Applicant has failed to provide any evidence, scientific reasoning and/or discussion to address how this limited set of circumstances could be extrapolated to the full scope of the instant claims, which are not limited in such a fashion (i.e., not limited to combinations of agents used in the Examples). For these reasons, Applicant is directed to MPEP §2144.08(II)(B), which states: “When considering whether proffered evidence is commensurate in scope with the claimed invention, Office personnel should not require the Applicant to show unexpected results over the entire range of properties possessed by a chemical compound or composition. See, e.g., *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987). Evidence that the compound or composition possesses superior

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and unexpected properties in one spectrum of common properties can be sufficient to rebut a *prima facie* case of obviousness. *Id.* For example, a showing of unexpected results for a single member of a claimed subgenus, or a narrow portion of a claimed range would be sufficient to rebut a *prima facie* case of obviousness if a skilled artisan 'could ascertain a trend in the exemplified data that would allow him to reasonably extend the probative value thereof.' *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980) (**Evidence of the unobviousness of a broad range can be proven by a narrow range when one skilled in the art could ascertain a trend that would allow him to reasonably extend the probative value thereof.**) But see, *In re Grasselli*, 713 F.2d at 743, 218 USPQ at 778 (Evidence of superior properties for sodium containing composition insufficient to establish the non-obviousness of broad claims for a catalyst with 'an alkali metal' where it was well known in the catalyst art that different alkali metals were not interchangeable and Applicant had shown unexpected results only for sodium containing materials); *In re Greenfield*, 571 F.2d 1185, 1189, 197 USPQ 227, 230 (CCPA 1978) (Evidence of superior properties in one species insufficient to establish the nonobviousness of a subgenus containing hundreds of compounds); *In re Lindner*, 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972) (one test not sufficient where there was no adequate basis for concluding the other claimed compounds would behave the same way).” (emphasis added)

Here, for the reasons described *supra*, it remains that the proffered data fails to be probative of the non-obviousness of the full scope of subject matter claimed because the data provided demonstrates unexpectedly greater activity under limited circumstances (i.e., two discrete combinations of agents) and, therefore, fails to be commensurate in scope with what is claimed. In order to rely upon unexpected results to patentably distinguish over the prior art, the present claims must be limited to those embodiments that are, in fact, unexpected, particularly in the absence of any further evidence, either in the form of data or persuasive scientific reasoning, as to why the proffered data would be reasonably extended to the broader scope of subject matter claimed with the reasonable expectation of achieving the

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same (or at least substantially similar) unexpected activity over this much broader range.

Applicant is reminded that, “The submission of objective evidence of patentability does not mandate a conclusion of patentability in and of itself. *In re Chupp*, 816 F.2d 643, 2 USPQ2d 1437 (Fed. Cir. 1987).” In view of this, and further in view of the fact that the evidence provided fails to be commensurate in scope with the claimed subject matter for the reasons *supra*, the totality of the evidence of non-obviousness fails to outweigh the evidence of obviousness as set forth *supra* when all of the evidence is considered.

Note, for clarity of the record, that the synergistic and/or unexpected activity using the two combinations exemplified in the instant specification (i.e., (1) paclitaxel and cytokine inducer or (2) paclitaxel, carboplatin and cytokine inducer) *are* probative of non-obviousness, since each combination demonstrated a much greater tumor mass reducing property over the chemotherapeutic agent(s) alone.

For these reasons, and those made of record *supra*, rejection of claims 15 and 18 is proper.

Conclusion

Rejection of claims 15 and 18 is proper.

No claims of the present application are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the

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mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds/
Patent Examiner, Art Unit 1614

April 15, 2008

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614